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Comparison Studies on the Percolation Thresholds of Binary Mixture Tablets Containing Excipients of Plastic/Brittle and Plastic/Plastic Deformation Properties

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ABSTRACT

Percolation theory has been used with great interest in understanding the design and characterization of dosage forms. In this study, work has been carried out to investigate the behavior of binary mixture tablets containing excipients of similar and different deformation properties. The binary mixture tablets were prepared by direct compression using lactose, polyvinyl chloride (PVC), Eudragit RS 100, and microcrystalline cellulose (MCC). The application of percolation theory on the relationships between compactibility, P_{max}, or compression susceptibility (compressibility), γ, and mixture compositions reveals the presence of percolation thresholds even for mixtures of similar deformation properties. The results showed that all mixture compositions exhibited at least one discreet change in the slope, which was referred to as the percolation threshold. The PVC/Eudragit RS100 mixture compositions showed significant percolation threshold at 80% (w/w) PVC loading. Two percolation thresholds were observed from a series of binary mixtures containing similar plastic deformation materials (PVC/MCC). The percolation thresholds were determined at 20% (w/w) and 80% (w/w) PVC loading. These are areas where one of the components percolates throughout the system and the properties of the tablets are expected to experience a sudden change. Experimental results, however, showed that total disruption of the tablet physical properties at the specified percolation thresholds can be observed for PVC/lactose mixtures at 20–30% (w/w) loading while only minor changes in the tablets' strength for PVC/MCC or PVC/Eudragit RS 100 mixtures were observed.

Key Words: Percolation theory; Binary mixture; Direct compression; Compactibility; Compression susceptibility.

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INTRODUCTION

The confusion and complexity in understanding the powder compression process has lead to studies being focused on individual materials. Since many tablets are a compressed mixture of several materials, the compaction properties of such mixtures are directly affected by the properties of the individual components. Compaction of a mixture of two powder materials may allow for studies of the behavior of individual powder and interactions between particles. This is usually carried out by means of direct compression. Apart from understanding the influence of powder properties of drugs on compaction, the mixing of two or more excipients may also optimize properties of such compacts.

Fell[1] illustrates two ways in which compaction properties of binary mixtures can be investigated. One is by examining the problem theoretically and then comparing the predictions with practical results. The second way is by investigating the compaction properties of mixtures of well-characterized materials and finding the common trends. Many workers have investigated compaction properties of binary mixture tablets. These were carried out by mixing materials of different deformation properties. For example, lactose, sucrose, and dicalcium phosphate are known to have brittle fracture properties. On the other hand, sodium chloride, cellulose, and aspirin are materials of plastic deforming properties. Thus, the two main areas of interest in these investigations were on the tablet strength and the influence of mixture composition on pressure-density relationships. One implicit assumption that has been widely reported is that the strength of a compact is a reflection of the bonding that has occurred during compaction. This statement is generally accepted and has been used in reporting experimental results describing compact's strength, although other factors may be involved.

Newton, Cook, and Hollebon,[2] for instance, examined mixtures of dicalcium phosphate dihydrate and phenacetin and found that the tablets produced were higher strength when compared to the individual component strength. The results also showed that the effect is similar at several compaction pressures. Vromans and Lerk[3] showed that strength enhancement was achieved when mixtures of roller-dried β-lactose, anhydrous lactose, and dicalcium phosphate dihydrate with 25% cellulose (Sanacel 90) were compacted and compared to compacts of single components. The studies also highlight that addition of a plastic material to roller-dried β-lactose gives an unpredictable effect depending on the types of cellulose used. Later studies by Wells and Langridge[4] on binary mixture tablets found that better tablets were produced only when mixtures of microcrystalline cellulose and dicalcium phosphate dihydrate were at 66–99% and 10–33%, respectively. Stress relaxation studies on the tablets suggested that reduced plastic flow and work hardening of microcrystalline cellulose were responsible for this behavior. However, stronger tablets were produced when the binary mixtures contained up to 20% of acetaminophen. Sheikh-Salem and Fell[5,6] examined initial packing of lactose, sodium chloride, and their mixtures only to find that it caused a marked reduction in tensile strength.

One way to understand the pattern of tensile strengths for binary mixture tablets is by using the theory of percolation, which was introduced by Leuenberger et al.[7–9] The observations on the sudden changes on the properties of the tensile strengths in the above studies may be related to what is termed as ''percolation thresholds.'' When a tablet is formulated with two different materials, especially of different deformation properties, lower and/or upper percolation thresholds for such a compact can be defined. In binary mixture tablets, the percolation thresholds correlate to the critical concentration ratio of the two components. A significant disruption in the properties of the compact can be observed close to the percolation threshold, either physically or through significant changes on the strength of the tablets, and this effect is known as a critical phenomenon.

When two powder materials of brittle fracture property are mixed together or a single brittle powder material is mixed with another plastic deformation material to form compacts, one can expect to observe at least one percolation threshold to occur at a specific concentration of the mixtures. This can either be an increase or decrease in the tensile strength of the tablets. This is also made possible due to the gradual changes of the bonding properties in the tablets throughout the mixture compositions. The changes in shapes and sizes of brittle fracture particles and their interactions in terms of intermolecular forces with other materials of similar or different deformation properties after compression and the possible presence of solid bridges and mechanical interlocking between particles may contribute to such phenomenon.

If two materials of plastic deformation properties are mixed together to form compacts, one would assume that no significant or sudden changes in the mechanical properties of the compacts is expected throughout the concentrations. The argument is based on the theoretical

assumption that compacting plastic deformation materials will allow the formation of bonding in tablets due to the presence of intermolecular forces without any significant fracture in the physical state of the solid individual particles.[10] Each individual particle is plastically deformed and the intermolecular forces, especially van de Waals forces of attraction, between the particles are assumed to be dominant with minimum changes throughout the mixture compositions. However, if detailed and careful examination is carried out on several plastic/plastic deformation materials, as studies reported in the past, one may find some changes in the tablet's strength throughout the materials composition ratios. Whether these were the true percolation thresholds or not, it is open for discussion. For instance, studies on binary mixtures of aspirin P150/metamizol as well as aspirin FC/metamizol (plastic/plastic deformation mixtures) by Jetzer, Leuenberger, and Sucker[11] using Leuenberger's equation actually showed a significant change in the maximum tensile strength value at 20% (w/w) aspirin loading, which may indicate the possible presence of a percolation threshold. Similar observation can be seen for amylose/dried cellulose binary mixture tablets, which also showed a significant reduction in crushing strengths.[3] Another study done by Leuenberger[12] on sodium stearate/caffeine showed another significant change on maximum tensile strength at 30% (w/w) sodium stearate loading at compression stress of 51.6 and 103 MPa.

Thus, the aim of this article is to report the results of another comparison study on the percolation thresholds of binary mixture tablets containing excipients of plastic/brittle and plastic/plastic deformation properties, and discuss and offer a possible explanation for such phenomenon.

MATERIALS AND METHODS

Materials

Lactose (Pharmatose 200M, PFW Ltd., UK) and Ammonio Methacrylate Copolymer Type B NF (Eudragit RS 100, DUMAS Ltd., UK) were chosen as materials deforming mainly by fragmentation. Polyvinyl chloride (Evipol, European Vinyl Corporation, Runcorn, UK) and microcrystalline cellulose (Emcocel LP200, Penwest, Guilford, UK) were used as plastically deforming materials. Eudragit RS 100 was milled and sieved to the size of 180–240 μm. All other materials were sieved to obtain a similar particle range. Magnesium stearate was from BDH, UK.

Preparation of Tablets

A series of binary mixtures of PVC/Eudragit RS 100, PVC/microcrystalline cellulose, and PVC/lactose were made prior to compaction. Mixtures were made in the following ratios 0:100, 20:80, 30:70, 50:50, 70:30, 80:20, and 100:0 w/w of the respective materials. All binary mixtures were mixed using a Turbula Mixer (model T2C, Willy A. Bachofen, Switzerland) for 30 minutes. These mixtures were kept in a dessicator with 75% relative humidity for at least 24 hours before compaction. Compacts of 500 mg each were made from these mixtures using a 1.2-cm punch and die, lubricated by 1% w/v magnesium stearate in acetone, and compacted using a compression testing machine (Howden Universal Testing Machine, R P Howden, Leamington Spa, UK) at a crosshead speed of 0.2 cm/min. The powders were compressed at different compression pressures up to 240 MPa.

Tablet Properties

Overall tablet porosities were calculated from the tablet dimensions and the true particle density of the material (AccuPyc 1330, Micromeritics, Norcross, MA). Tensile strength of the tablets was determined using diametral compression by measuring the load to fracture the compacts across the diameter using the compression testing machine at 0.1 cm/min. Tensile strength was calculated from the formula:

$$\textit{Tensile Strength} = 2P/\pi DT$$

where P=the breaking load, D=tablet diameter, and T=its thickness.

Scanning electron photomicrographs of the tablets were taken using a Cambridge Stereoscan (Model 360, Cambridge Scientific Instruments, Cambridge, UK). The specimens were mounted on circular aluminium stubs and coated with gold prior to observation.

The interrelationship of compactibility and compressibility of the binary mixture powders was investigated using Leuenberger's equation:[6]

$$P = P_{max}[1 - \exp(-\gamma\sigma_c\wp_r)]$$

where P=deformation resistance, P_{max}=compactibility, at $\wp_r$, $\wp_r$=relative density, where $\wp_r = 1-\varepsilon$ and ε=porosity, σ_c=applied compression stress, and γ=compression susceptibility.

The compression parameters, i.e., compactibility, P_{max} and compression susceptibility, γ were determined simultaneously using nonlinear regression analysis

program (SPSS for Windows, Standard Version, Release 10.0.5.)

RESULTS AND DISCUSSION

Figure 1a–c show the relationships between the compactibility, P_{max} and mixture compositions for PVC/Eudragit RS 100, PVC/microcrystalline cellulose, and PVC/lactose. On the other hand, Fig. 2a–c show the relationships between the compression susceptibility, γ and mixture compositions for PVC/Eudragit RS 100, PVC/microcrystalline cellulose, and PVC/lactose. As expected, all plastic/brittle fractures exhibit at least one significant percolation threshold. In the case of PVC/Eudragit RS 100, the percolation threshold can be seen at 80:20 composition ratios. This is the point where the interparticle bonding between the particles of brittle fracture materials, i.e., Eudragit RS 100-Eudragit RS 100, dominates inside the tablet composition, taking over from the intermolecular forces of PVC-PVC particles (plastic deformation) and PVC-Eudragit RS100 particles. As a result, one can see the significant reduction in the compactibility, P_{max} values after 80:20 composition ratios due to the weaker in bonding between the resultant particles. This is in agreement in concept and pattern with the earlier works of Sheikh-Salem and Fell[6] on lactose and sodium chloride.

The PVC/lactose mixtures on the other hand, exhibited disruption in tablet properties when the amount of PVC was less than 50%. Thus, the 50:50 ratio of PVC/lactose is the critical concentration ratio of the two components. The tablets that consist of PVC/lactose of 20:80 and 30:70 composition ratios exhibit a capping phenomenon at the specified compression pressure. This would also indicate that the percolation threshold stands at 50:50 PVC/lactose mixture compositions. The incompatibilities between the two materials of different deformation properties at such composition ratios, however, differ from the earlier work of Jetzer, Leuenberger, and Sucker and Sheikh-Salem and Fell.[6,11] The difference in the relative densities, compression pressure, and low porosities of the starting materials may be responsible for the disagreement, although the plastic deformation/brittle fracture binary mixture tablets concept was similar.

What is so striking in this work is that PVC/microcrystalline cellulose mixtures exhibited two significant percolation thresholds at 20:80 and 80:20 composition ratios when the compactibility, P_{max} and compression susceptibility, γ values from Leuenberger's equation were calculated using the nonlinear regression analysis. Since PVC and microcrystalline

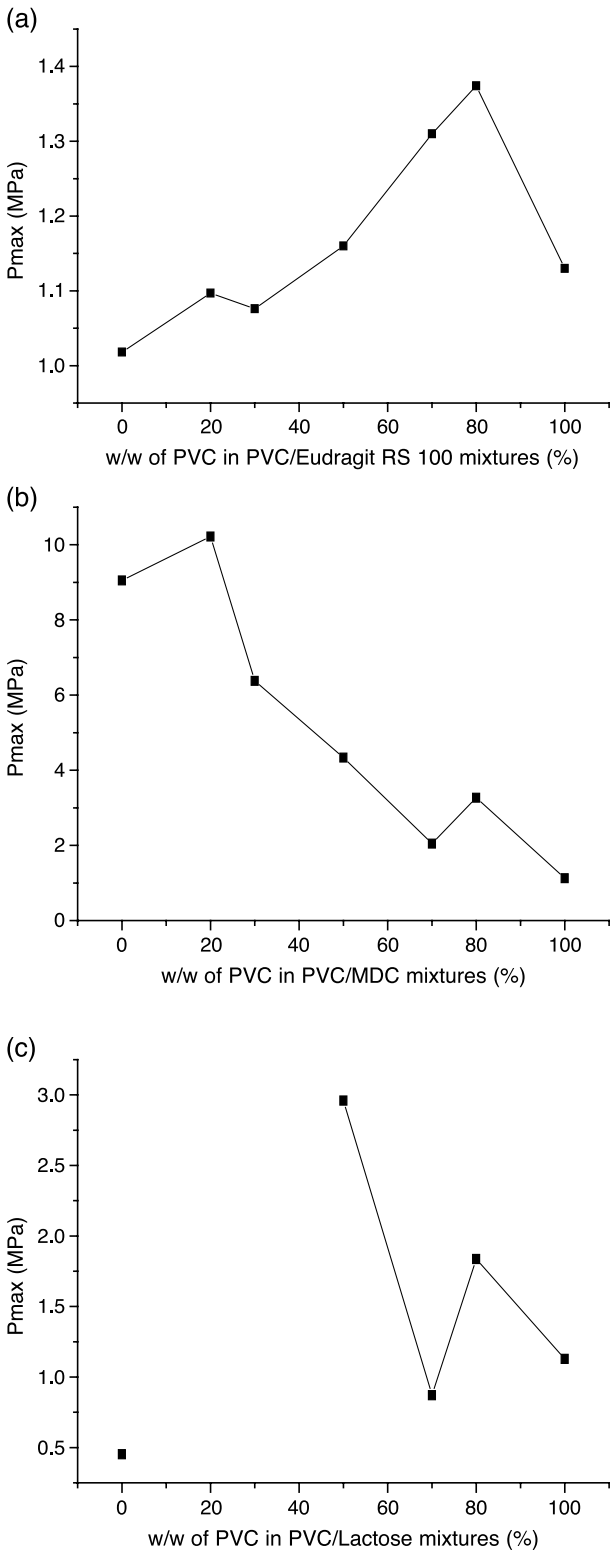


Figure 1. The relationships between the compactibility, P_{max} and mixture compositions: a=PVC/Eudragit RS 100, b=PVC/microcrystalline cellulose, and c=PVC/lactose.

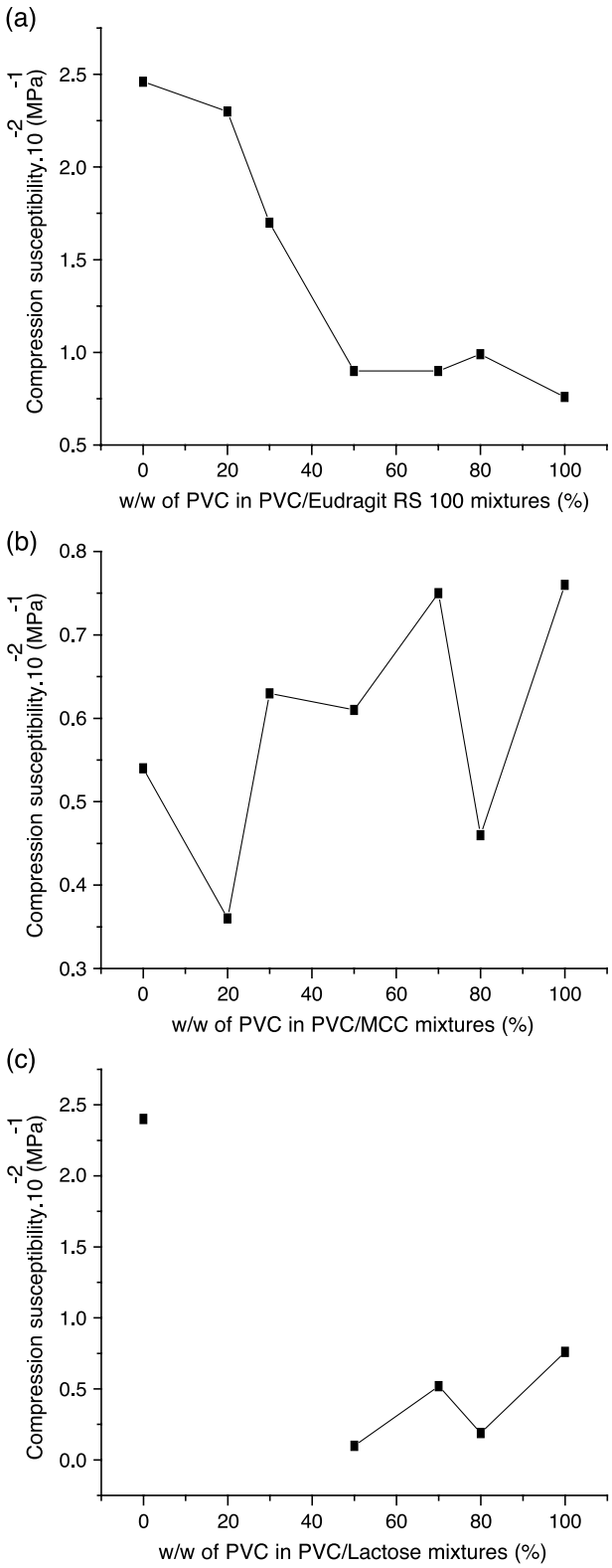


Figure 2. The relationships between the compression susceptibility (γ) and mixture compositions: a=PVC/Eudragit RS 100, b=PVC/microcrystalline cellulose, and c=PVC/lactose.

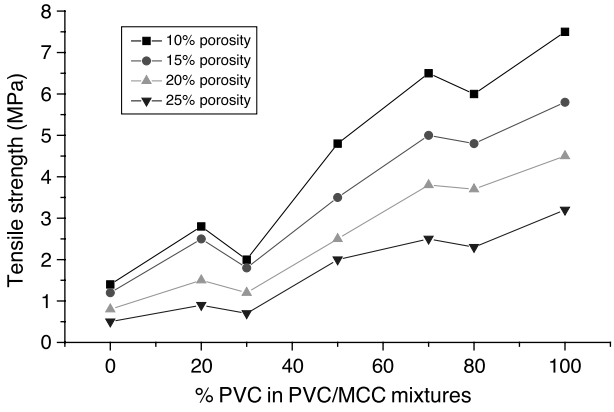


Figure 3. The relationship between the tensile strength and mixture compositions in PVC/MCC mixtures at constant porosities.

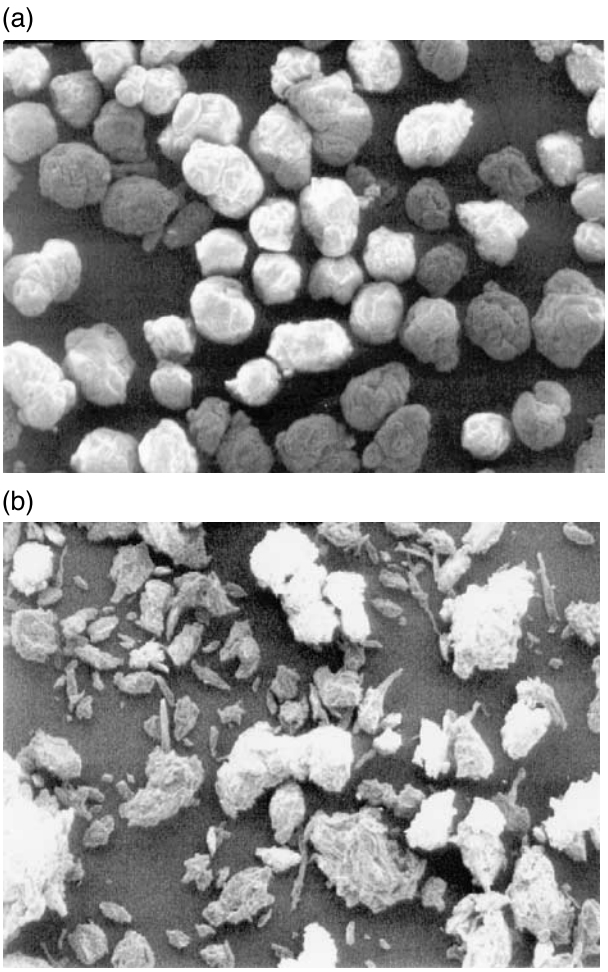
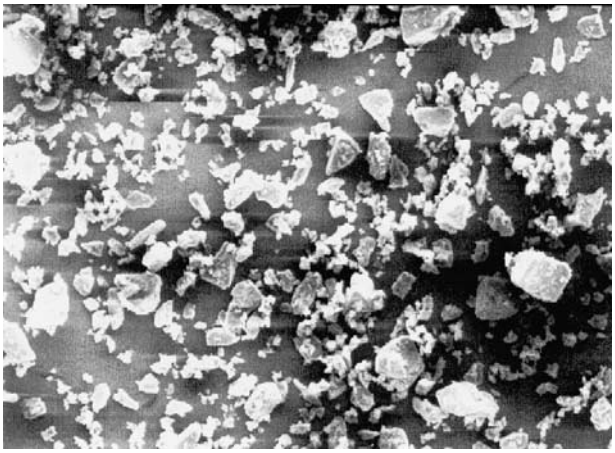


Figure 4. Scanning electron photomicrographs of: a=PVC particles, b=MCC particles, c=Lactose particles, and d=Eudragit RS 100 particles.

(c)



(d)

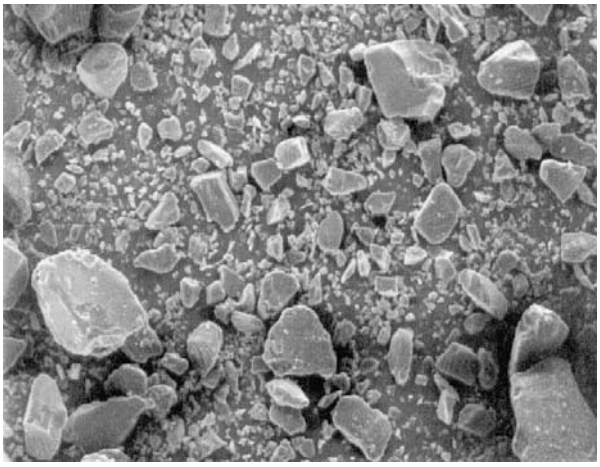
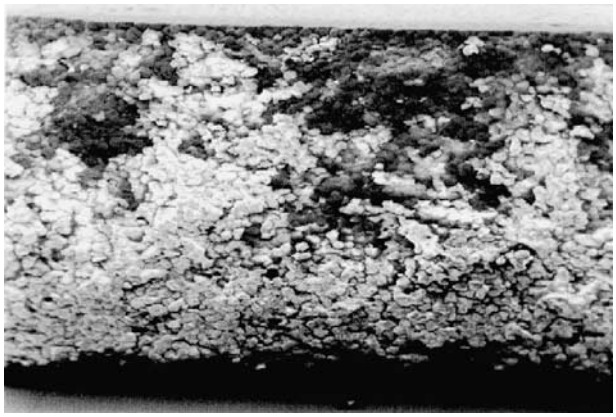


Figure 4. Continued.

cellulose were both considered as plastic deformation properties, this result was quite surprising. However, if the elasticity and plasticity properties together with particle sizes and shapes are taken into account, this behavior could be explained. Rime et al.[13] examined the compressibility and compactibility of PVC powders and found that the powder exhibits a higher resistance to volume reduction. The plasticity indices are rather low, which suggests that a high elastic component is present in the deformation of PVC particles. At the same time, the strain recovery is as significant as evidenced by both the high values of porosity at ejection and elastic recovery. In other words, the PVC particles possess high elastic rather than plastic deformation properties. On the other hand, microcrystalline cellulose has been known to have high plastic deformation properties as reported by Bolhuis and Chowhan.[15] David and Augsburger[14] suggested that plastic flow is an important factor affecting the compressibility of microcrystalline cellulose. Comparing the particle shapes, Fig. 3 shows that PVC particles are more uniform spherical and agglomerates while microcrystalline cellulose consists of smaller particles of needlelike shape, but larger particles are irregular and more symmetrical. Considering all these factors, characteristics and properties of the two materials, it is possible to deduce that the presence of percolation thresholds in the PVC/microcrystalline cellulose could be due to the high elasticity property of PVC particles and its shape combining with the irregular sizes and shapes of plastic deformation property of microcrystalline cellulose. These would contribute to the decrease of compression susceptibility, γ, of the mixture at 20:80 and 80:20 composition ratios. On the other hand, the compactibility, P_{max} of the mixtures shows a sudden increase, which suggest that the strong bonding interactions of PVC-microcrystalline cellulose

(a)



(b)

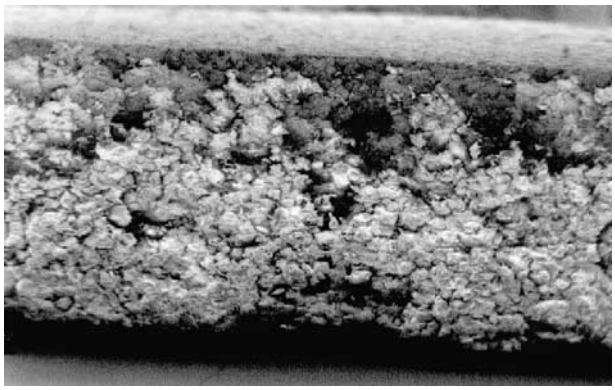


Figure 5. Scanning electron photomicrographs of cross-sections through the tablets: a=PVC, b=microcrystalline cellulose, c=Eudragit RS 100, and d=lactose.

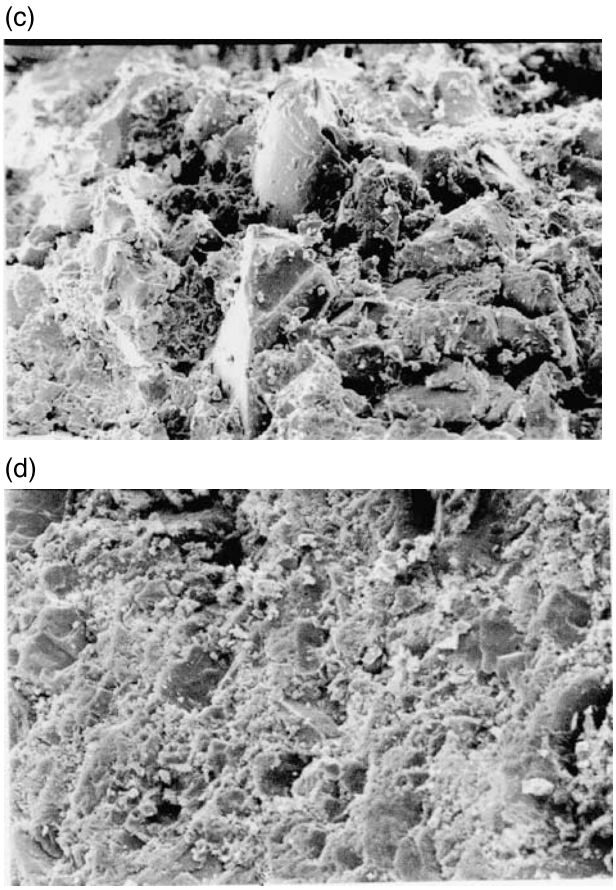


Figure 5. Continued.

may occur between the particles. The bonding interactions could be due to the hydrogen bonds between hydrogen groups on the plastically deformed materials[10,16] and ionic bonding due to the negatively charged ion of the PVC molecular structure. However, experimental results showed that the changes were not so evident in the sense that they would not disrupt the physical properties of the tablet such as capping as in the brittle fracture materials. This is probably due to the fact that the intermolecular forces at such a composition ratio were sufficient to prevent the physical structure of the tablet from collapsing. Nevertheless, plotting tensile strength against % concentration of PVC in PVC/microcrystalline cellulose at constant porosities reveals sudden changes in the tensile strength at 20% and 80% PVC loading, as shown in Fig. 4.

Figure 5a–d show sections through the fracture surfaces of tablets prepared from PVC, microcrystalline cellulose, Eudragit RS 100, and lactose compressed at 72 MPa. Differences in density from the upper to lower regions can be seen in PVC and microcrystalline cellulose but not with Eudragit RS 100 and lactose. In order to investigate the presence of percolation thresholds in PVC/microcrystalline cellulose and

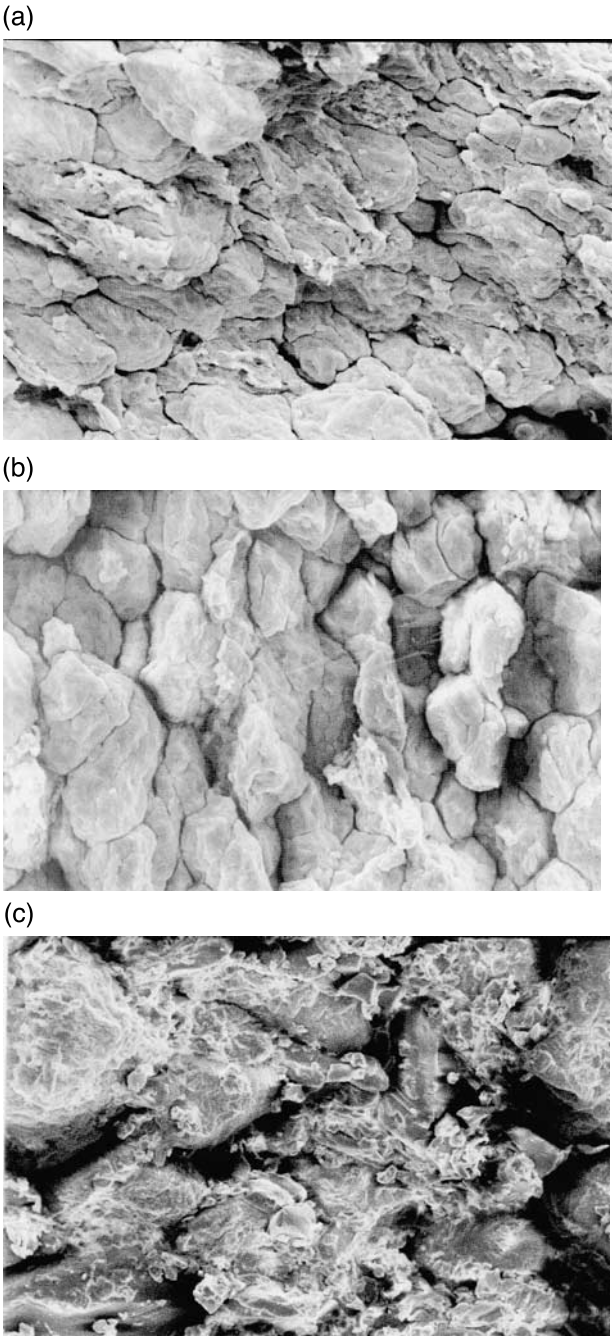


Figure 6. Scanning electron photomicrographs of cross-sections through the tablets: a=20:80 PVC/microcrystalline cellulose, b=80:20 PVC/microcrystalline cellulose, and c=80:20 PVC/Eudragit RS 100.

PVC/Eudragit RS 100 tablet mixtures, scanning electron photomicrographs were carried out.

Figure 6a–c show sections through the fracture surfaces of tablets of similar compression pressure prepared from composition ratios of 20:80 and 80:20 of PVC/microcrystalline cellulose and 80:20 PVC/Eudragit RS 100. The fibrous structure of microcrystalline cellulose can be clearly distinguished from the PVC particles. However, examining the particles' structure from the surface to the core of the tablets showed that the materials do not completely deform under pressure except at the surface of the tablets. This is in agreement with a study reported earlier.[17] For the PVC/Eudragit RS100 mixture, the fragments of Eudragit particles can be seen stuck into the PVC particles. This suggests that the intermolecular forces between the particles and mechanical interlocking are responsible for the bonding in the tablets.

The compression parameters for the nonlinear regression analysis of each binary mixture compositions are given in Table 1a–c. The overall results show that the compactibility (P_{max}) and compressibility (γ) for the binary mixture compositions are statistically significant ($p < 0.05$).

Table 1. The compression parameters for the nonlinear regression analysis of each binary mixture composition.

a

PVC (weight %)	MCC (weight %)	P_{max} (MPa)	95% Confidence limits	$\gamma \cdot 10^{-2}$ (MPa^{-1})	95% Confidence limits	No. of measurement points	R^2
0	100	9.05	8.03–10.07	0.54	0.00–0.01	5	0.99
20	80	10.22	7.86–12.57	0.36	0.00–0.01	5	0.99
30	70	6.38	5.28–7.48	0.63	0.00–0.01	6	0.98
50	50	4.34	2.86–5.83	0.61	0.00–0.01	5	0.95
70	30	2.05	1.34–2.75	0.75	0.00–0.01	5	0.92
80	20	3.27	1.23–5.32	0.46	0.00–0.01	6	0.92
100	0	1.13	0.42–1.83	0.76	0.00–0.02	6	0.77

b

PVC (weight %)	Eudragit (weight %)	P_{max} (MPa)	95% Confidence limits	$\gamma \cdot 10^{-2}$ (MPa^{-1})	95% Confidence limits	No. of measurement points	R^2
0	100	1.02	0.76–1.27	2.46	0.00–0.05	7	0.95
20	80	1.09	0.76–1.44	2.30	0.01–0.05	5	0.42
30	70	1.08	0.91–1.23	1.70	0.01–0.03	5	0.87
50	50	1.16	0.64–1.67	0.90	0.00–0.02	6	0.84
70	30	1.31	0.98–1.64	0.90	0.00–0.02	5	0.93
80	20	1.37	0.69–2.05	0.99	0.00–0.02	6	0.76
100	0	1.13	0.42–1.83	0.76	0.00–0.01	6	0.77

c

PVC (weight %)	Lactose (weight %)	P_{max} (MPa)	95% Confidence limits	$\gamma \cdot 10^{-2}$ (MPa^{-1})	95% Confidence limits	No. of measurement points	R^2
0	100	0.45	0.24–0.66	2.34	0.02–0.07	7	0.95
20	80	–	–	–	–	–	–
30	70	–	–	–	–	–	–
50	50	2.96	4.47–10.39	0.10	0.19–0.40	6	0.79
70	30	0.87	0.35–1.39	0.52	0.00–1.03	5	0.83
80	20	1.84	1.96–5.63	0.19	0.30–0.68	5	0.75
100	0	1.13	0.42–1.83	0.76	0.00–0.02	6	0.77

CONCLUSION

The study thus confirms the existence of percolation thresholds in the binary mixture tablets containing excipients of plastic deformation/brittle fracture, while in plastic/plastic deformation properties, the possibility of its occurrence cannot be ignored. Leuenberger's equation shows the presence of percolation thresholds for binary mixture tablets of plastic/plastic deformation materials and can be confirmed when examining the tensile strength and porosity relationship. The findings in this study may provide new understanding in terms of particle to particle bonding interactions, especially between materials of plastic deformation properties.

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